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CD30+ Lymphoproliferative Disorders of the Skin

Maxwell B. Sauder, MD, FRCPC [Cutaneous Oncology Fellow], **John T. O'Malley, MD, PhD [Clinical Instructor]**, and **Nicole R. LeBoeuf, MD, MPH [Assistant Professor, Clinical Director, The Center for Cutaneous Oncology]**

Department of Dermatology, Brigham and Women's Hospital, Boston, MA, U.S.A.; The Center for Cutaneous Oncology, Dana Farber Cancer Institute, Boston, MA, U.S.A; Harvard Medical School, Boston, MA, U.S.A.

SYNOPSIS

Primary cutaneous CD30+ lymphoproliferative disorders encompass lymphomatoid papulosis (LyP), primary cutaneous anaplastic large cell lymphoma (pcALCL) and indeterminate cases. LyP is a benign disorder characterized by recurrent crops of several to hundreds of papulonodules, red or violaceous in color and measuring up to 20mm, usually on the trunk and extremities. Patients with LyP are at increased risk of a secondary malignancy that may be diagnosed before, during or after the diagnosis of LyP and thus should receive ongoing surveillance. pcALCL is characterized by a solitary red to violaceous nodule or tumor greater than 20mm and may occur anywhere on the body. Secondary cutaneous ALCL must be excluded for any patient initially presenting with a cutaneous lesion of ALCL. LyP is benign, limited to the skin and self-resolves with a 5-year survival rate of 100%; pcALCL is usually limited to the skin and responsive to directed therapies, with a 5-year survival of over 95%. Aggressive systemic or multi-agent chemotherapeutic regimens should be avoided.

Keywords

CD30+; Cutaneous lymphoproliferative disorders; Lymphomatoid papulosis; Primary cutaneous anaplastic large cell lymphoma; Secondary cutaneous anaplastic large cell lymphoma

Introduction

Cluster of differentiation 30 (CD30), a 120 kDa type I transmembrane glycoprotein of the tumor necrosis factor receptor superfamily member 8 (TNFRSF8) gene and previously known as Ki-1 antigen, is a cell surface cytokine receptor present on activated T- and B-cells. Upon T-cell activation, CD28 and other co-stimulatory receptors, including CD30 are

Correspondence to: Nicole R. LeBoeuf.

AUTHOR CONTACT INFORMATION: 375 Longwood Avenue, Boston, MA, 02115

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upregulated. CD30 expression requires CD28 or IL-4 receptor (IL-4R) signalling and, when CD30 is activated, downstream signalling augments T-cell proliferation at low levels and regulates T-cell survival.[1,2]

CD30 interacts with CD30 ligand (CD30L, CD153, TNFSF8), a 40-kDa type II membrane-associated glycoprotein belonging to the TNF family[1,2], that is expressed on activated T-cells, primarily CD4 T-cells of both Th1 and Th2 phenotype, as well as on a subset of accessory cells[1,3,4] and B cells[5,6]. CD30 signalling ultimately leads to nuclear factor (NF)-kB activation through both TNFR-associated factor (TRAF) 2-dependent and TRAF2-independent pathways that can inhibit effector cell activity, promote apoptosis or promote survival depending on the cell type and different intracellular signaling pathways activated.[7,8,9] For example, ligation of CD30 signals can downregulate the cytotoxic effector molecules Fas ligand, perforin, granzyme B and inhibit cytotoxicity.[4] CD30 signalling also promotes apoptosis by strongly inhibiting the expression of the oncogene c-myc and upregulating Fas (TNFRSF6), death receptor 3 (TNFRSF25) and TNF-related apoptosis-inducing ligand (TNFSF10, TRAIL).[10] In addition to increasing the cell's susceptibility to apoptosis, CD30 signalling strongly upregulates chemokine receptor 7 (CCR7), a homing molecule that enhances the cell's ability to home to lymphoid organs. A variety of causes have been implicated in the induction of CD30 expression in human cutaneous reactive and neoplastic lymphocytic processes including infectious, exogenous, inflammatory and lymphoproliferative disorders (Table 1).

CD30 is expressed in a subset of B-cell lymphoid malignancies (approximately 20%) and T-cell lymphoid malignancies (30%), including the most common CD30+ lymphoid malignancies, Hodgkin's lymphoma and systemic anaplastic large cell lymphoma.[11,12,13] However, there is a subset of non-Hodgkin's lymphoma where the disease process is contained within the skin with no other evidence of blood and lymph node involvement. This article will focus on the diagnosis, clinical presentation and management of these primary cutaneous CD30 lymphoproliferative disorders.

Primary cutaneous CD30+ lymphoproliferative disorders (LPD) comprise a spectrum of conditions with similar histologic and molecular features, but different clinical presentations. According to the World Health Organization (WHO) and European Organization for Research and Treatment (EORTC) classification, this group accounts for 20% of all cutaneous lymphomas, second most common cutaneous T-cell lymphoma (CTCL) behind mycosis fungoides.[14] The primary cutaneous CD30+ LPD include lymphomatoid papulosis (LyP), primary cutaneous anaplastic large cell lymphoma (pcALCL) and borderline or indeterminate cases.

pcALCL and LyP can be thought of as a clinical spectrum where indeterminate cases may have clinical and histological features of either (Figure 1). As will be discussed, patients with LyP may have a co-existing secondary lymphoma, including pcALCL and therefore both conditions may exist simultaneously in an individual patient. Indeterminate cases tend to eventually develop clinical features of either LyP or pcALCL over time. Historical diagnoses that may capture the full spectrum of CD30 LPD include *regressing atypical histiocytosis* or *indolent primary cutaneous Hodgkin lymphoma.*[15]

Lymphomatoid papulosis (LyP)

Epidemiology

Macaulay first described lymphomatoid papulosis in 1968, aptly referring to the recurring self-healing eruption as clinically benign but histologically malignant.[16] LyP is the most common CD30+ LPD, more common than pcALCL. Best estimates suggest that there are approximately 1.2 to 1.9 cases per million persons of LyP in the US.[17] It presents in men more often than women with an average age of onset of 35 to 45 years[18]. (Table 2). The etiology of LyP is not known although hypotheses implicating reactive phenomena inducing over expression of CD30 have been proposed.

Prognosis

The 5-year survival of patients with LyP is close to 100%, despite the increased risk of secondary malignancy that may be diagnosed before, during or after the diagnosis of LyP.[14] This secondary malignancy risk can affect 5–30% of LyP patients[19,20,21,22] although, several larger retrospective series indicated that the incidence of a secondary malignancy may actually be closer to 40–60%.[23,24] Mycosis fungoides (MF) and ALCL are the first and second most commonly associated malignancies respectively, accounting for over 90% of secondary malignancies in one series.[24] The majority of the secondary cases of MF are early stage, IA or IB. Other secondary hematologic malignancies that have been reported to occur with LyP are listed in Table 3. Male sex and advanced age are risk factors associated with a higher risk of a secondary LPD; additional factors are noted in Table 4.

Presentation

Clinically, LyP is characterized by recurrent crops of red to violaceous papules and nodules measuring up to 20mm but typically 3–10mm in diameter (Table 5). Patients often present with lesions in various stages due to the recurrent and successive crops of papules and nodules, with hyperpigmented macules and varioliform scars in the background (Figure 2). The number of lesions can range from a few to hundreds at a time. Lesions typically are generalized with the majority on the trunk and extremities. Localized presentations of crops within regional areas or in agminated plaques have also been described.[25,26] Approximately half of all patients are asymptomatic while others experience pruritus and/or pain secondary to ulceration, crusting and central necrosis.[27] LyP is not associated with systemic symptoms. The resolving lesions often display post-inflammatory hypo- or hyperpigmented macules. Necrotic lesions may leave varioliform scars, usually smaller than the original papules. Typically, lesions spontaneously resolve within 1–4 months[28], most often between 2 and 8 weeks. The self-healing nature of LyP is the critical clinical pearl required for making the diagnosis, particularly in the face of a concerning pathology report. It is hypothesized that the feature of resolution may be associated with CD30L expression on the neoplastic cells, causing the CD30 expressing cells to undergo apoptosis either through CD30-CD30L inhibition of neoplastic cell growth and/or increased sensitivity of the neoplastic cells to Fas-FasL mediated apoptosis.[8] Patients with LyP may develop recurrent crops over several months or for decades, with cases reported to last over 40 years.[18]

Differential diagnosis

With histologic evidence of a CD30+ infiltrate, all entities in Table 1 should be considered. Coupled with a clinical presentation of recurrent self-resolving crops of papulonodules, the main differential diagnoses include:

1. Pityriasis lichenoides
2. Borderline CD30 LPD
3. Cutaneous anaplastic large cell lymphoma
4. Reactive lymphoid hyperplasia (lymphocytoma cutis) secondary to:
    a. Arthropod assault
    b. Scabies
    c. Medications
    d. Herpes simplex virus
    e. Varicella zoster virus

Pathology

When considering LyP, skin biopsy is recommended for histologic and immunohistochemical (IHC) evaluation to classify the cellular subtypes and rule out infectious entities. DNA should be sent for T-cell gene rearrangement polymerase chain reaction (PCR) to assess for clonality.

There are currently 5 generally accepted histologic subtypes of LyP (A-E), as well as a recently proposed 6th subtype (F) (Table 6). CD30+ T-cell lymphocytes are the hallmark of all histologic types of LyP, although type B has variable positivity, reported to range from 0 to 77% of the infiltrate.[29] Subtypes may occur concurrently within the same biopsy or within different specimens taken from the same patient. Other rare pathological variants include γ/δ-type[30] and LyP with 6p25.3 re-arrangement-type[31]. The significance of the γ/δ-variant is unknown. The 6p25.3-type is described as biphasic with small-medium lymphocytes in the epidermis and larger pleomorphic lymphocytes in the dermis. Clinically, this variant presents in older individuals (mean 75 years) and has a higher male predominance (3:1 M:F ratio). Otherwise, the course follows the same natural history of all other variants of LyP.

The clinical significance of the histological subtypes remains unclear, with rare exceptions. As noted, type B can be CD30 negative and histologically resemble MF. In this setting, the clinical morphology and behaviour is then required to distinguish the two and render a diagnosis of LyP. Additionally, subtypes B and C have been shown to be associated with a higher risk of secondary malignancy.[24]

Immunohistochemistry is required to characterize the infiltrate (Table 7). The majority of LyP cases are CD4+ and CD45RO+; however, type D, type E and LyP in children are CD4− CD8+.[29] CD45RO helps to differentiate LyP type D from aggressive epidermotropic CD8+ CTCL with the former being CD45RO+ and the latter being CD45RO-.[14]

T-cell receptor (TCR) gene rearrangement demonstrates clonality in 40–100% of cases of LyP, despite its benignity.[29] The significance of the clonality in the risk of developing a secondary malignancy remains to be determined. The majority of cases have α/β T-cell receptor (TCR) clones with few reports of γ/δ TCR clonality, particularly in type D LyP.[32]

Work-up

The evaluation of a patient with a suspected or biopsy confirmed case of CD30 LPD is outlined in Figure 3 and Table 8. Despite being a disorder visible on exam, definitive diagnosis is often delayed by 1 to 3 years.[33] In most cases, a diagnosis of LyP can be rendered based on history and thorough dermatologic physical exam alone, with biopsy providing diagnostic confirmation. For accuracy of diagnosis and to exclude those entities described in the differential diagnosis, the following investigations are recommended:

1. Skin biopsy, including IHC and TCR gene rearrangement
2. Complete blood count (CBC) with differential
3. Lactate dehydrogenase (LDH)
4. Serology for HTLV 1 and 2 for patients in endemic areas
5. Imaging, if indicated based on history or exam
6. Lymph node biopsy, if enlarged

It is suggested to biopsy 2 or more papules that are inflammatory but, have not yet undergone necrosis.

Treatment

Management of LyP depends on clinical severity and symptoms. Indications to treat include cases that are diffuse or progressive, are physically symptomatic or lead to disfigurement from significant scarring or pigmentary change.

With limited disease burden, active non-treatment may be appropriate and considered first-line. Patients can be reassured that treatment has not been reported to alter the natural course of LyP or the risk of developing a secondary malignancy.[33]

If active treatment is required, a therapeutic ladder for treating LyP is outlined in Table 9. As with any therapy, and of particular importance in the setting of a recurrent, self-resolving disorder, the benefits of the treatment must outweigh the associated risks. The goal of treatment is to prevent new outbreaks, accelerate resolution of lesions and prevent secondary scarring and pigmentary change. With all treatments, recurrence occurs in over 40% of patients, typically within weeks of discontinuing or decreasing treatment.[34] While Table 9 lists many therapeutic options, the majority of patients with few lesions are managed with potent topical steroids at the first sign of a new papule; those with more diffuse disease respond to low dose methotrexate or phototherapy. Additional agents are rarely required and multi-agent chemotherapy regimens are not indicated or effective at inducing a prolonged remission in this benign disorder. The use of systemic chemotherapy has been associated with rapid recurrence of LyP either during or after treatment.[34]

Regardless of treatment plan, patients living with LyP should have life-long follow-up to monitor for the development of a secondary hematologic malignancy. Additionally, any lesion that is persistent and/or greater than 2cm should be biopsied to rule out concomitant ALCL or other secondary neoplasms.

Cutaneous anaplastic large cell lymphoma (cALCL)

cALCL can be divided into primary cutaneous ALCL (pcALCL) and secondary cutaneous ALCL (scALCL). scALCL is systemic ALCL with skin involvement, where the skin is the most common extra-nodal site.[35] Please see Dai Chihara and Michelle A. Fanale's "Management of Anaplastic Large Cell Lymphoma," in this issue for a more in depth discussion of Systemic ALCL.

Epidemiology

Patients with pcALCL have an older median age of onset (60 years) than their LyP counterparts, and it affects males more than females at a ratio of 3:1 (Table 2).[20] scALCL has a bimodal age distribution that varies with anaplastic lymphoma kinase (ALK) expressivity; patients with ALK positive scALCL present at a median age of 34 years; whereas, those that are ALK negative present at a median age of 58 years.[36]

Prognosis

Similar to LyP, pcALCL has a favourable prognosis with greater than 95% survival at 5 and 10 years. With draining lymph node involvement in greater than 1 nodal basin, survival decreases to 76–96% at 5 years; however, involvement of nodes in a single draining basin has a prognosis similar to patients with disease isolated to the skin.[20] Conversely, patients with systemic ALCL have a less favourable prognosis; those with ALK positive disease tend to be younger and have a 5-year survival of 70% while ALK negative disease tends to occur in older patients and has a 49% 5-year survival. Extra-nodal involvement of sALCL, such as cutaneous involvement, is a poor prognostic sign.[36]

Clinical

In contrast to the successive crops of small self-healing papulonodules of LyP, pcALCL most often presents with a solitary or local group of nodules or tumors, larger than 2cm. Patients describe a rapidly growing, red to violaceous nodule or tumor that may ulcerate (Figure 4).[15] While alarming, these lesions are generally asymptomatic and patients are systemically well, without fevers, chills, fatigue, night sweats or weight loss. Such B symptoms should raise suspicion of a systemic lymphoma.

While the majority of patients present with a solitary lesion, approximately 25% of cases of pcALCL present with a localized group of nodulo-tumors and up to 22% of cases may have multifocal (usually two) lesions at different anatomic sites.[20] Regression, either partial or total, is variable and occurs in approximately 28% of cases with a range of 0—44%. This feature may highlight indeterminate cases or those that are confused with LyP. Spread of pcALCL to extracutaneous sites is uncommon, but has been reported in approximately 13% of cases with a range of 0–24% depending on the series.[37]

Importantly, systemic ALCL commonly presents with B symptoms and approximately 20% of cases of sALCL will develop skin lesions (Figure 5).[38] The lesions tend to be multifocal or generalized in contrast to pcALCL.

Pathology

In the majority of cases, routine histopathology of pcALCL demonstrates a dense dermal nodular infiltrate with sheets of atypical large anaplastic lymphocytes. The epidermis is generally uninvolved unless there is ulceration present. Anaplastic cells refer to cells with irregular nuclei that are often horseshoe-shaped, have eosinophilic nucleoli and abundant cytoplasm.[14] Importantly, the sheets of anaplastic lymphocytes cannot be distinguished from LyP type C histologically and differentiation of the two entities is made based on the clinical presentation. In 20–25% of cases, pcALCL presents with a non-anaplastic pleomorphic or immunoblastic histopathology. In these cases, which show a heterogeneous inflammatory infiltrate including neutrophils and eosinophils, differentiation from LyP type A is made based on the clinical presentation. Interestingly and sometimes complicating the clinicopathologic correlation, cases of pcALCL with LyP-like histopathology are more likely to completely regress.[20]

By definition, at least 75% of the tumor cells must express CD30.[39] In pcALCL, anaplastic lymphoma kinase (ALK) is almost always negative. Importantly, in scALCL, ALK is positive in only 50% of cases[40] and therefore, ALK negativity does not rule out scALCL. Additionally, cutaneous lymphocyte antigen (CLA) is generally positive in pcALCL whereas epithelial membrane antigen (EMA) is typically negative.[20] In contrast, expression of CLA is usually negative and EMA is positive in scALCL. (Table 7) Please see Dai Chihara and Michelle A. Fanale's "Management of Anaplastic Large Cell Lymphoma," in this issue for additional details on the pathology of scALCL.

Differential diagnosis

Again, with histologic evidence of a CD30+ infiltrate, all entities in Table 1 should be considered. However, the main differential in nodulo-tumors > 2cm that variably self-resolve are:

1. scALCL
2. LyP
3. Transformed mycosis fungoides
4. Other systemic lymphomas including Adult T-cell leukemia-lymphoma (ATLL) or Hodgkin disease with cutaneous involvement
5. Nodular reactive lymphoid hyperplasia due to arthropod bite, medication or infection

Work-up

The work-up for cALCL is more extensive than LyP owing to the greater possibility of extracutaneous involvement. A comprehensive history and physical exam along with a biopsy of suspicious lesions remain the first steps in diagnosis. Similar to LyP, the skin

biopsy should be performed and examined for histopathologic appearance, classification of the infiltrate using IHC, and T-cell gene rearrangement to assess for clonality.

Following the establishment of a diagnosis of cALCL based on clinical and pathologic features, systemic involvement must be ruled out. Lack of B-symptoms is supportive of a diagnosis of pcALCL; however, complete evaluation is recommended to evaluate for extracutaneous disease of all subsets. The following are recommended:

1. CBC with differential
2. LDH
3. Contrast enhanced computed tomography (CT) with positron emission tomography (PET/CT) is preferred over CT of the chest, abdomen and pelvis
4. Biopsy of any avid lymph nodes and those larger than 1.5cm
5. Bone marrow biopsy is considered in the setting of diffuse or multifocal tumors, abnormal hematologic exam or documented extracutaneous disease.

Treatment

The approach to pcALCL therapy is determined by clinical presentation (Table 10: Treatment of pcALCL). The mainstay of treatment for solitary to few lesions of pcALCL is radiotherapy or surgical excision. Given the inherent difficulty in determining margins for cutaneous LPD, radiotherapy is preferred. There are no recommended surgical margins for pcALCL. The optimal dose for radiotherapy also has not been identified but generally 36–40 Gy in 2–3 fractions are used with a margin of 2–3cm, with complete responses ranging from 86% to 100%.[41]

Historically treatment for multiple lesions involved multi-agent chemotherapy. Based on the overall prognosis, natural history of pcALCL and high rates of relapse after systemic treatment (40–70%)[34,37], multi-agent chemotherapy is not considered first line; there does not appear to be added benefit beyond less toxic alternatives. Low-dose (less than 25mg/week) methotrexate is considered first-line for multifocal pcALCL where radiotherapy is not feasible.[28] Brentuximab vedotin has been used off-label for multifocal, refractory, extracutaneous or relapsed pcALCL[42] and is increasingly being used early in the treatment course. It is currently FDA approved for treatment of patients with systemic ALCL after failure of at least one prior multi-agent chemotherapy regimen.[43] In the case of pcALCL with nodal involvement to a single region, radiotherapy to the primary site and nodal basin may be employed.

Conclusion

CD30 lymphoproliferative disorders of the skin are comprised of a spectrum of benign and malignant diseases encompassing LyP, pcALCL and borderline cases. Accurate diagnosis of these conditions requires a thorough history and complete dermatologic and nodal exam, noting the natural course of the lesions and the status of lymph nodes and systemic symptoms. The accurate description of the morphology, distribution and behaviour of lesions is crucial for reaching the correct diagnosis. While all cases of CD30 LPD may look

histologically malignant, their behaviour and knowledge of the natural course of LyP and pcALCL (5-year survival of 100% and greater than 95% respectively) allows clinicians to avoid aggressive treatment with high recurrence rates. Importantly, ongoing surveillance of these patients is still required to monitor for secondary malignancy with LyP and recurrence or extracutaneous spread of ALCL.

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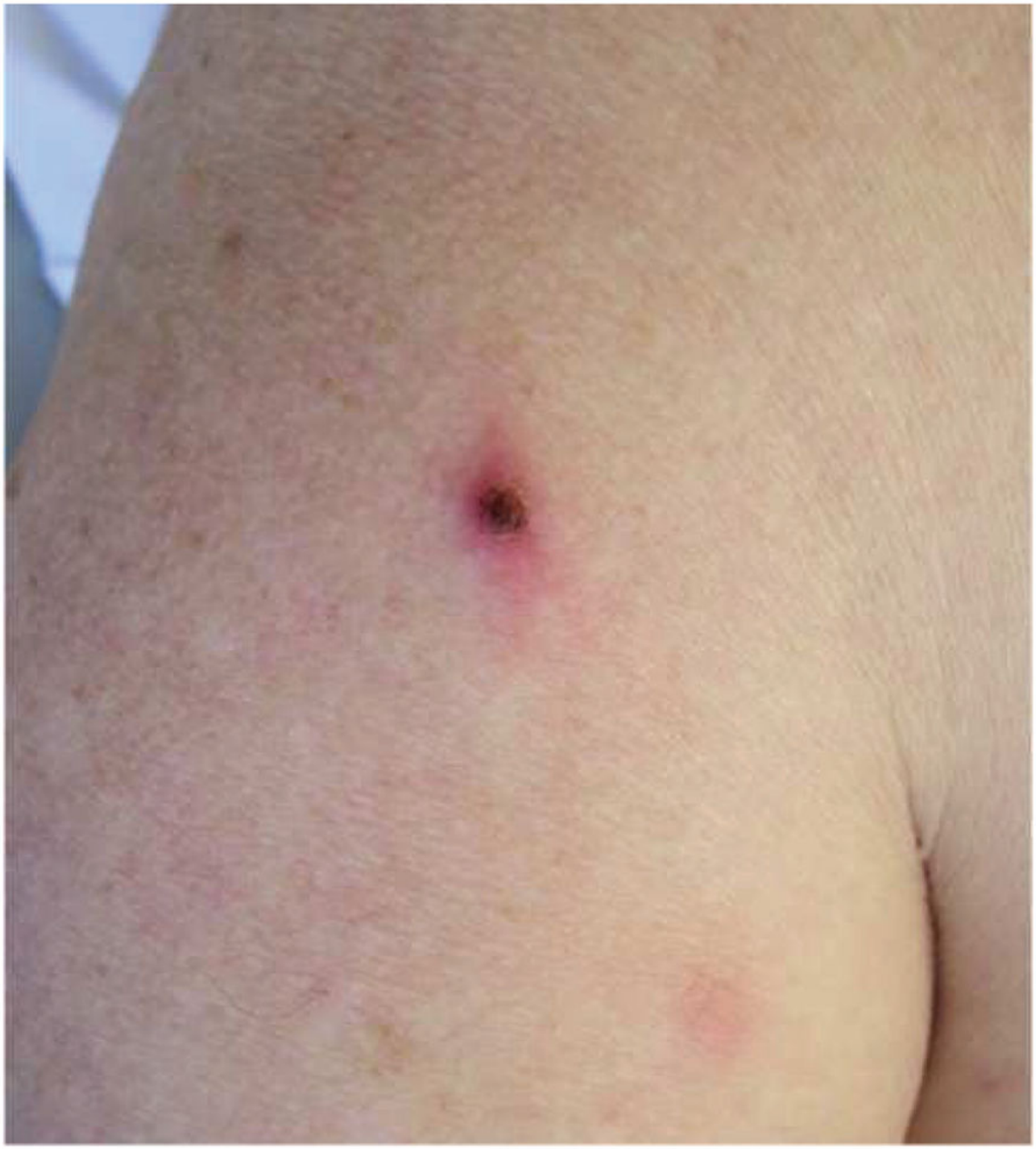
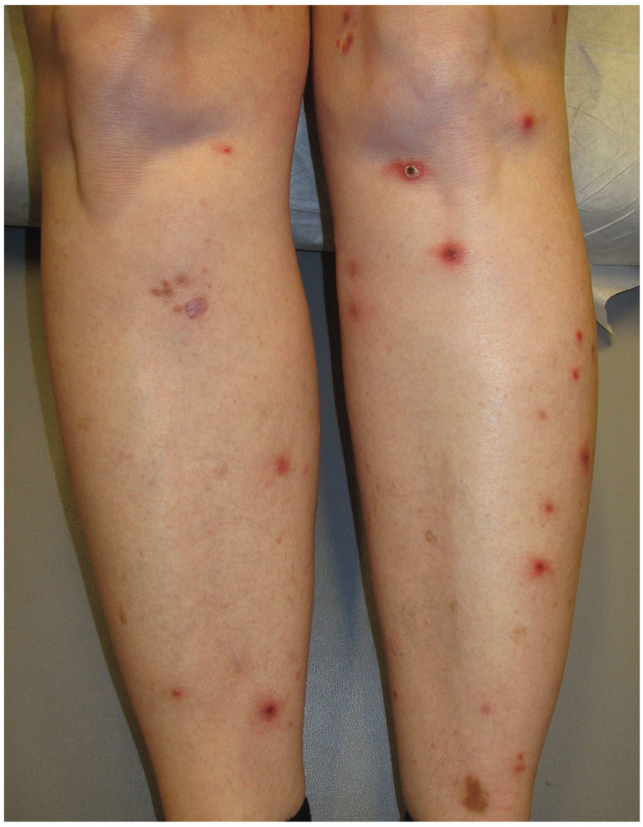
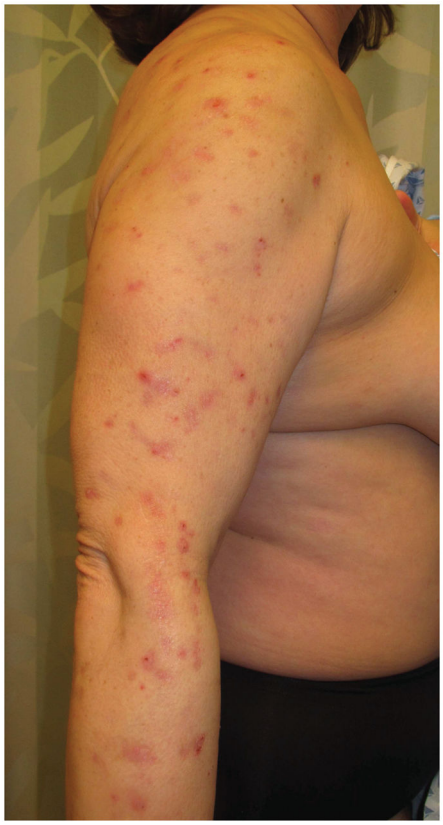
KEY POINTS

- Primary cutaneous CD30+ lymphoproliferative disorders encompass a spectrum of benign to malignant phenotypes including lymphomatoid papulosis (LyP), primary cutaneous anaplastic large cell lymphoma (pcALCL) and borderline cases.
- LyP is characterized by recurrent crops of several to hundreds of red to violaceous papulonodules measuring up to 20mm, usually on the trunk and extremities.
- pcALCL is characterized by a solitary or localized red to violaceous nodulotumor greater than 20mm that may occur anywhere on the body.
- Patients with LyP are at increased risk of secondary malignancy, most often mycosis fungoides or ALCL, may be diagnosed before, during or after the diagnosis of LyP and should undergo ongoing surveillance.
- Patients presenting with cutaneous ALCL should be worked-up to ensure it is primary cutaneous and not secondary cutaneous involvement of systemic ALCL.

Figure 1.
Primary cutaneous CD30+ LPD clinical spectrum







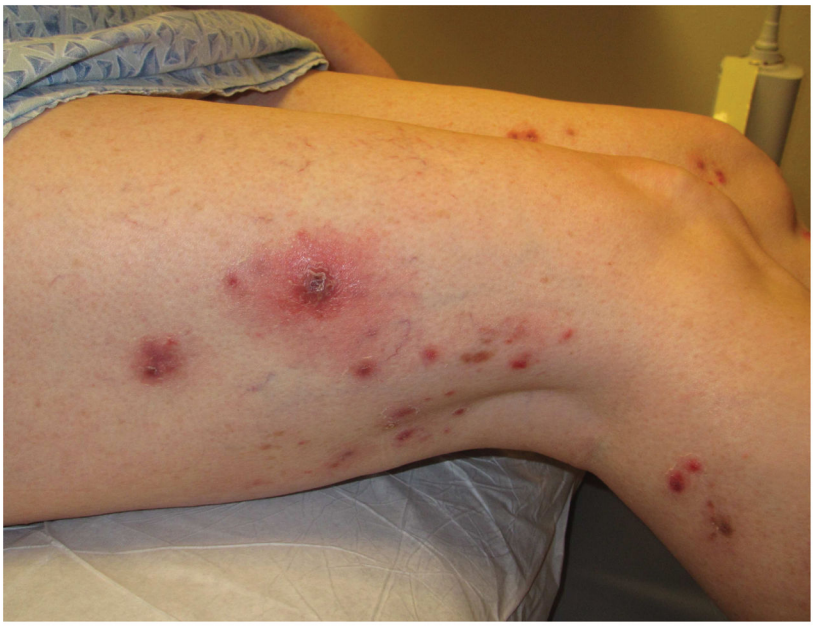


Figure 2.
Clinical presentations of lymphomatoid papulosis (LyP)

2A – Typical lesion of LyP: 6mm violaceous papule with necrotic center

2B, C – Crops of LyP in various stages of evolution

2D – Inflamed lesion of LyP, with a surrounding crop of more typical lesions

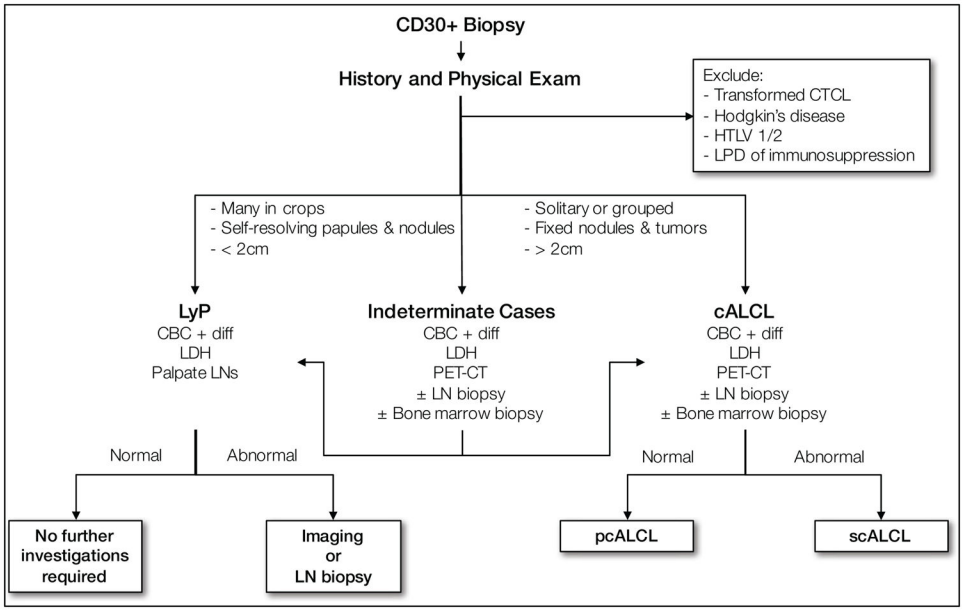
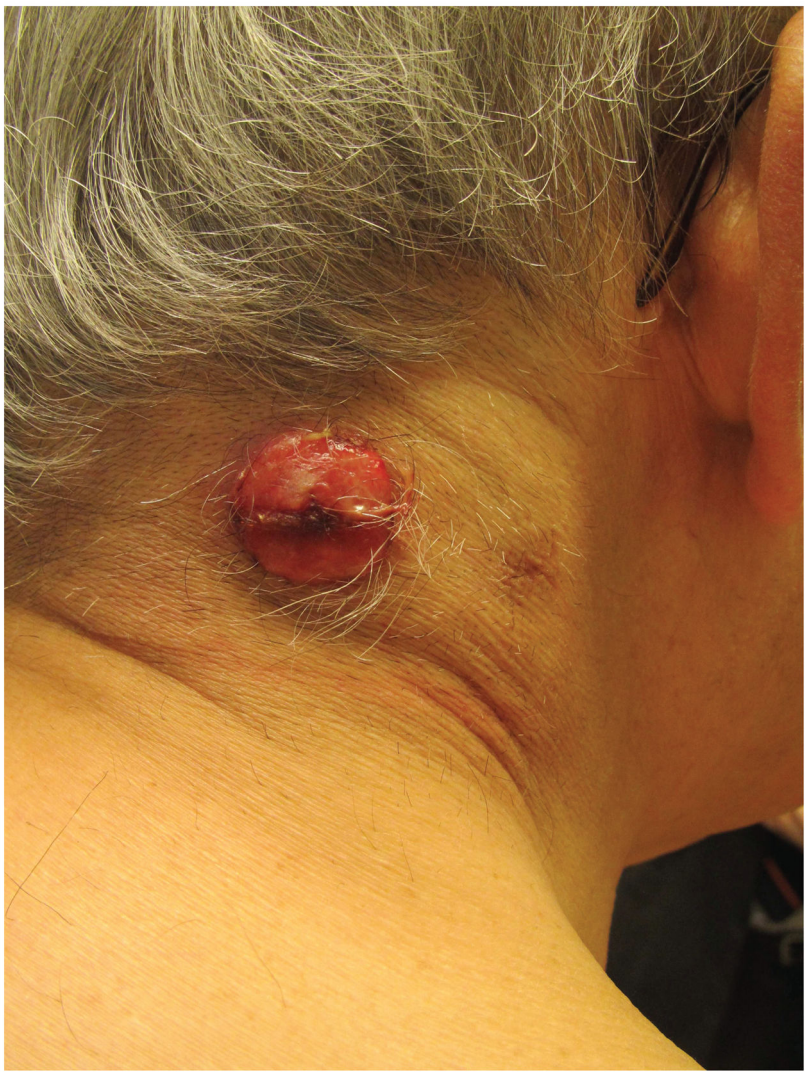
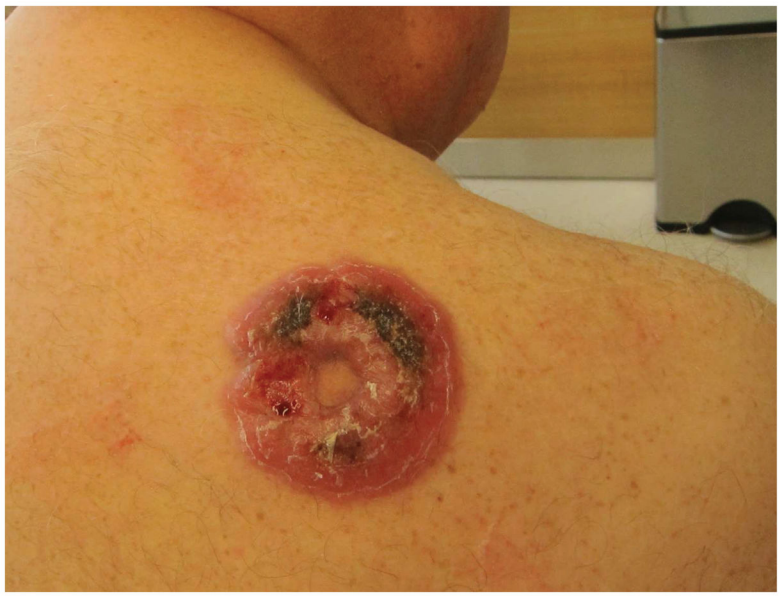
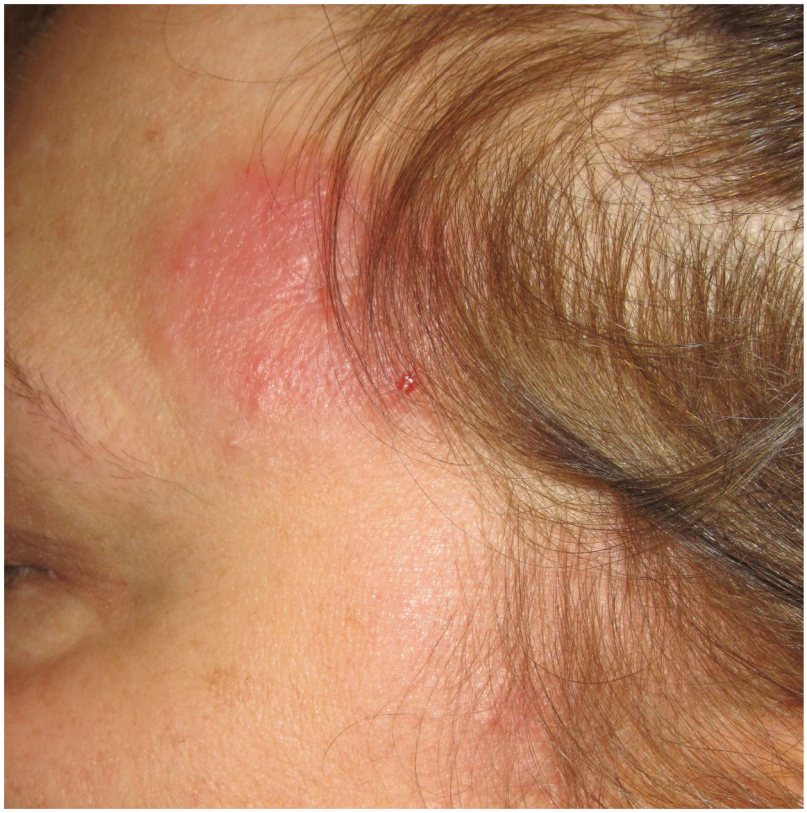


Figure 3.
Diagnosis algorithm for primary cutaneous CD30+ LPD







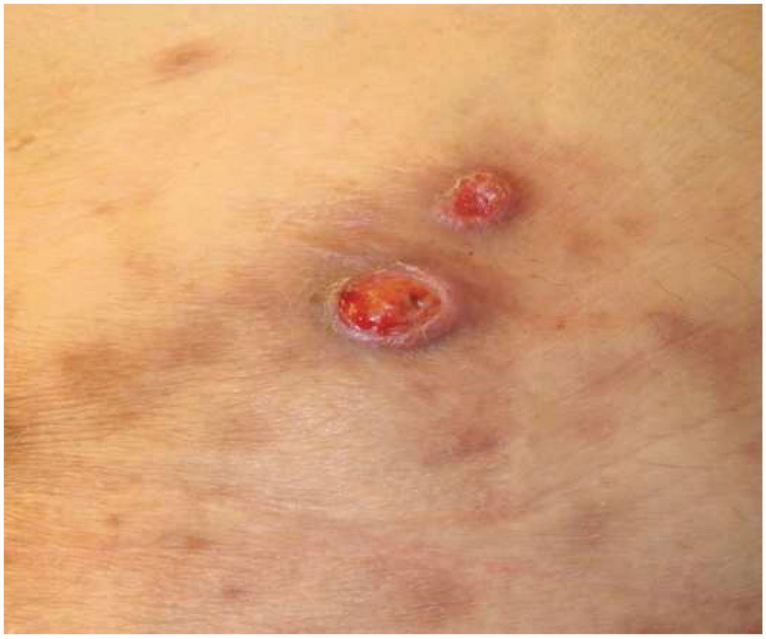


Figure 4.
Clinical presentations of primary cutaneous ALCL

4A – Typical pcALCL tumour: Red, friable 2.5cm tumor, well-defined with central crusting

4B -- pcALCL tumor measuring 5.5 x 7.2cm with central clearing and hemorrhagic crust

4C – Early pink plaque of pcALCL

4D – Multifocal, localized and ulcerative pcALCL

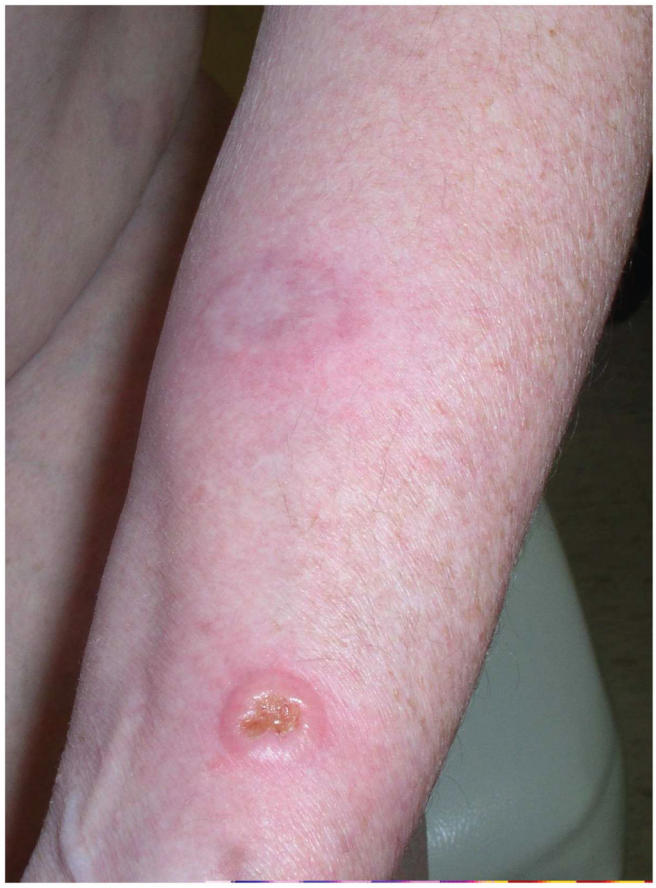


Figure 5.
Cutaneous involvement of ALK- systemic ALCL, with annular plaques and tumors. Note evidence of scarring at prior sites on the arm and trunk.

TABLE 1

CD30+ Lymphocytic Disorders

Neoplastic	Lymphomatoid papulosis (LyP) Primary cutaneous anaplastic large cell lymphoma (pcALCL) br1>Systemic cutaneous anaplastic large cell lymphoma (scALCL) Mycosis fungoides or Sezary syndrome with CD30+ large cell transformation Cutaneous Hodgkin's disease CD30+ large B-cell lymphoma Epstein Barr virus (EBV)+ hydroa vacciniforme-like T-cell lymphoma Human T-cell Lymphotropic virus type 1 (HTLV-1) associated adult T-cell lymphoma/leukemia Eruptive keratoacantomas
Exogeneous	Drug-induced reactive lymphoid hyperplasia[44,45,46,47,48,49,] Insect bite reaction[50] Scabies infestation[51]
Infection associated	EBV[52] HTLV-1/2 Mycobacteria[53] Herpes simplex virus (HSV)[50] Human immunodeficiency virus[54] Other infections: leishmaniasis, syphilis, varicella zoster virus, molluscum contagiosum virus and parapox virus**Error! Bookmark not defined.**
Inflammatory conditions	Pityriasis lichenoides • Pityriasis lichenoides et varioliformis acuta • Pityriasis lichenoides chronica Eruption of lymphocyte recovery[55] Atopic dermatitis[56]

Adapted from: LeBoeuf NR, McDermott S, Harris NL. Case records of the Massachusetts General Hospital. Case 5–2015. A 69-year-old woman with recurrent skin lesions after treatment for lymphoma. N Engl J Med. 2015 Feb 12;372(7):650–9, with permission.

TABLE 2

Epidemiology of LyP and pcALCL

	LyP	pcALCL
% of primary cutaneous lymphomas	12%	8%
5-year survival	100%	>95%
Incidence	1.2–1.9 cases per 1,000,000	Unknown
M:F Ratio	1.4:1	3:1
Median Age of Diagnosis (years)	45.5	60
Age range (years)	4–88	16–89

Data from references 14, 20, 58, 59

TABLE 3

Secondary malignancies associated with LyP

Most common (>90% of cases)	Mycosis fungoides, stage IA or IB > later stage Anaplastic large cell lymphoma, primary cutaneous > nodal Hodgkin's disease
Rare reports (<10% of cases)	Chronic lymphocytic leukemia Acute myeloid leukemia B-cell lymphoma T-cell large granular lymphocytic leukemia Multiple myeloma Myelodysplastic syndrome

Data from de Souza A, el-Azhary RA, Camilleri MJ, Wada DA, Appert DL, Gibson LE. In search of prognostic indicators for lymphomatoid papulosis: a retrospective study of 123 patients. J Am Acad Dermatol. 2012 Jun;66(6):928–37 and Wieser I, Tetzlaff MT, Torres Cabala CA, Duvic M. Primary cutaneous CD30(+) lymphoproliferative disorders. J Dtsch Dermatol Ges. 2016 Aug;14(8):767–82.

TABLE 4

Risk factors for developing a secondary malignancy with LyP

Male sex (2.5–2.8 times more likely)[23]
History of EBV either clinical or serological (4.8 times more likely)[23]
Histological subtypes B and C (2.66 odd ratio [OR] and 2.83 OR, respectively)[24]
LyP with clonal T-cell receptor gene rearrangement (5.7–7.55 OR)[22]
Advanced age (1.05 OR per year)[57]

TABLE 5

Clinical features of LyP and pcALCL

	LyP	**pcALCL**
Size	5–10mm	>20mm
Number of lesions	Several to hundreds	Solitary or localized
Distribution	Trunk and limbs	Anywhere
Duration of lesions	3–8 weeks	>12 weeks
Self-resolving	100%	28% (0–44%)
Extracutaneous disease	0%	13% (0–24%)

Data from references 14, 18, 38.

Table 6

Histological morphologies of LyP

Type	% of cases	Histologically Mimicks	Description
A	47–82%	Hodgkin lymphoma Transformed MF	• Large Reed-Sternberg-like atypical lymphocytes • Wedge-shaped heterogeneous infiltrate with lymphocytes, neutrophils, eosinophils and histiocytes
B	4–17%	MF	• Epidermotropic band-like infiltrate • Small irregular lymphocytes • Cerebriform nuclei
C	7–22%	ALCL	• Sheets or clustered infiltrate • Large atypical lymphocytes • Few inflammatory cells
D	~8%	Primary cutaneous aggressive CD8+ cytotoxic T-cell lymphoma (TCL), PLC/PLEVA Pagetoid reticulosis Cutaneous gamma/delta TCL	• Epidermotrophic infiltrate • CD8+ • Small to medium atypical lymphocytes
E	~0.6%	Angiocentric: Extranodal NK/T-cell lymphoma, nasal type Cutaneous gamma/delta TCL ALCL variant with angiocentric and/or angiodestructive growth	• Small- to medium-sized lymphocytes • Angiocentric: CD8+ infiltrating walls of small to medium-sized vessels • Vasculitis: fibrin, thromboses and extravasation of red blood cells
F[58]	5–10%	Folliculotropic: Folliculotropic MF Pseudolymphoma Connective tissue diseases	• Perifollicular infiltrate • Medium to large lymphoid cells • Follicular mucinosis • Neutrophils within infundibula
Mixed	4–9%		• More than 1 histological type in the same patient or lesion

Data from references 20, 24, 30, 58, 69

Table 7

Immunohistochemical profile of LyP and ALCL

	LyP	pcALCL	scALCL
Clonality	40–100%	>90%	~90%
CD30	+ (type B, variably)	>75% + (required for diagnosis)	+
CD56	~10%	12–75%	+ (worst prognosis)
Bcl-2	−	30%	+
Cytotoxic molecules: TIA-1, Granzyme B or Perforin	+	~50%	+
ALK	−	Rare	50%
CLA	+	Variable	−
EMA	−	−	+
t(2;5)(pq23;q35) translocation	−	<10%	70–75%

Data from references 30, 59, and 60

Table 8

CD30+ Work-up

LyP	pcALCL	scALCL	
History			
Spontaneous regression	✓	✓	x
Previous Lymphoid Neoplasms (MF, nodal ALCL or Hodgkin lymphoma)	✓	x	✓
Immunosuppression	x	x	x
B symptoms	x	x	✓
Physical exam			
Solitary lesion	x	✓	✓
Many lesions	✓	x	✓
Patches/plaques of MF	✓	x	x
Enlarged Lymph Nodes	x	x	✓
Hepatosplenomegaly	x	x	✓
Laboratory investigations			
Abnormal CBC with differential	x	x	✓
Abnormal LDH	x	x	✓
Serology for HTLV-1/2	x	x	x
Other investigations			
Contrast enhanced CT ± PET of chest, abdomen and pelvis or whole body integrated PET-CT	x	✓	✓
Bone marrow aspirate or biopsy	x	Only if radiologic evidence of extracutaneous disease	✓
Lymph node biopsy if > 1.5cm	x	If >1.5cm palpable or evidence on imaging	✓

Adapted from: Kempf W, Pfaltz K, Vermeer MH, et al. EORTC, ISCL, and USCLC consensus recommendations for the treatment of primary cutaneous CD30-positive lymphoproliferative disorders: lymphomatoid papulosis and primary cutaneous anaplastic large-cell lymphoma. Blood 2011; 118:4024, with permission.

TABLE 9

Treatment of LyP

1st Line	Active non-treatment Topical corticosteroids Class I-III for trunk and extremities; Class IV, V for face, genitals and axillae Phototherapy Methotrexate, 5–25mg/week *
2nd Line	Topical tacrolimus Topical nitrogen mustard Topical retinoids (bexarotene) Topical carmustine
3rd Line	Radiotherapy * Imiquimod 5% cream Interferon-a, Interferon-g Brentuximab vendotin (anti-CD30 monoclonal antibody) ** Antiobiotics: tetracyclines, penicillin, erythromycin Sulfones Surgical excision *

* Generally accepted regimens include starting doses 7.5–12.5mg per week, increasing as tolerated every 8–12 weeks until clear up to 25mg per week. Once control has been maintained for 8–12 weeks with no new lesions, the dose is titrated down in a similar fashion to the lowest dose attainable without flares.

** For larger, refractory and persistent lesions

*** For multifocal disease

Adapted from: Klein, RS, Singer E, Junkins-Hopkins JM, Vittorio CC, Rook AH, Kim EJ. “141: Lymphomatoid Papulosis.” Treatment of skin disease: Comprehensive therapeutic strategies. By Lebwohl, M. G., Heymann, W., Berth-Jones, J., & Coulson, I. 4th ed. Edinburgh: Saunders. 2014. 430–434, with permission.

TABLE 10

Treatment of pcALCL

Solitary or grouped lesions	**Local radiotherapy, first line** **Excision**
Multifocal	Low dose methotrexate (5–25mg/week) Systemic retinoids Pralatrexate Brentuximab vedotin Monitor for spontaneous resolution
Extracutaneous spread	Nodal radiation, if single basin Brentuximab vedotin Low dose methotrexate (5–25mg/week) Pralatrexate Multi-agent doxorubicin based chemotherapy

Data from National Comprehensive Cancer Network. Non-Hodgkin lymphomas version 3.2016 (https://www.nccn.org/professionals/physician_gls/PDF/nhl.pdf).